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The Immunoglobulin E-Toll-Like Receptor Network

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Key Words
Immunoglobulin E · IgE receptor · Toll-like receptors

Abstract
Allergens and microbial antigens impact on effector cells and antigen-presenting cells in allergic diseases. Allergens bind specifically to immunoglobulin E (IgE) linked to the high-affinity receptor for IgE (FcεRI) and stimulate a cascade of cellular events. This leads to the release of mediators of allergic reactions by effector cells on the one hand and antigen uptake, presentation and T cell priming by antigen-presenting cells on the other hand. In contrast, microbial antigens are recognized by pattern-recognition receptors (PRRs) of the innate immune system, to which Toll-like receptors (TLRs) belong. In view of the high number of microbial antigens, allergens and other soluble ligands in the cellular microenvironment in vivo, it is very likely that not only separate, but also concomitant stimulation of both receptor types, i.e. FcεRI and TLRs, occurs frequently under physiological conditions and in particular in the context of allergic and infectious disorders. Thus, interaction of TLRs with FcεRI and regulation of the IgE synthesis is of critical immunological importance, since it might profoundly modify the activation state of cells and the nature of the evolving immune responses. Current knowledge about the cross talk of TLRs with FcεRI- and IgE-related immune responses is discussed herein.

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Introduction

The high-affinity receptor for immunoglobulin E (IgE) (FcεRI) binds IgE and is of critical importance in a plethora of immune responses in allergic diseases [1]. Tetrameric FcεRI (αβ2γ-chain) complex is expressed by effector cells, while a trimeric (α2γ) variant which lacks the β-chain is expressed by monocytes, myeloid dendritic cells, plasmacytoid dendritic cells (PDC) and eosinophils [1]. The α-chain consists of an extracellular part, which is responsible for IgE binding, while the γ-chain dimers, which are covalently bound and contain immunoreceptor tyrosine-based activation motifs (ITAMs), are essential for downstream signaling. The β-chain, which is the only integral part of the tetrameric FcεRI variant, stabilizes the receptor complex on the cell surface and acts as an amplifier of FcεRI-mediated downstream signaling [2].

Toll-like receptors (TLRs) are pattern-recognition receptors composed of an extracellular part, with leucin-rich repeats, which allow binding of pathogen-associated molecular patterns. Further on, TLRs consist of a transmembrane domain and an intracellular Toll/interleukin-1 (IL-1) receptor domain (TIR), responsible for cell signaling [3]. TLRs are linked to adaptor molecule myeloid differentiation factor 88 (MyD88) and are capable of inducing activation of nuclear factor (NF)-κB and NF-κB-related genes [4]. So far, ten different TLRs have been

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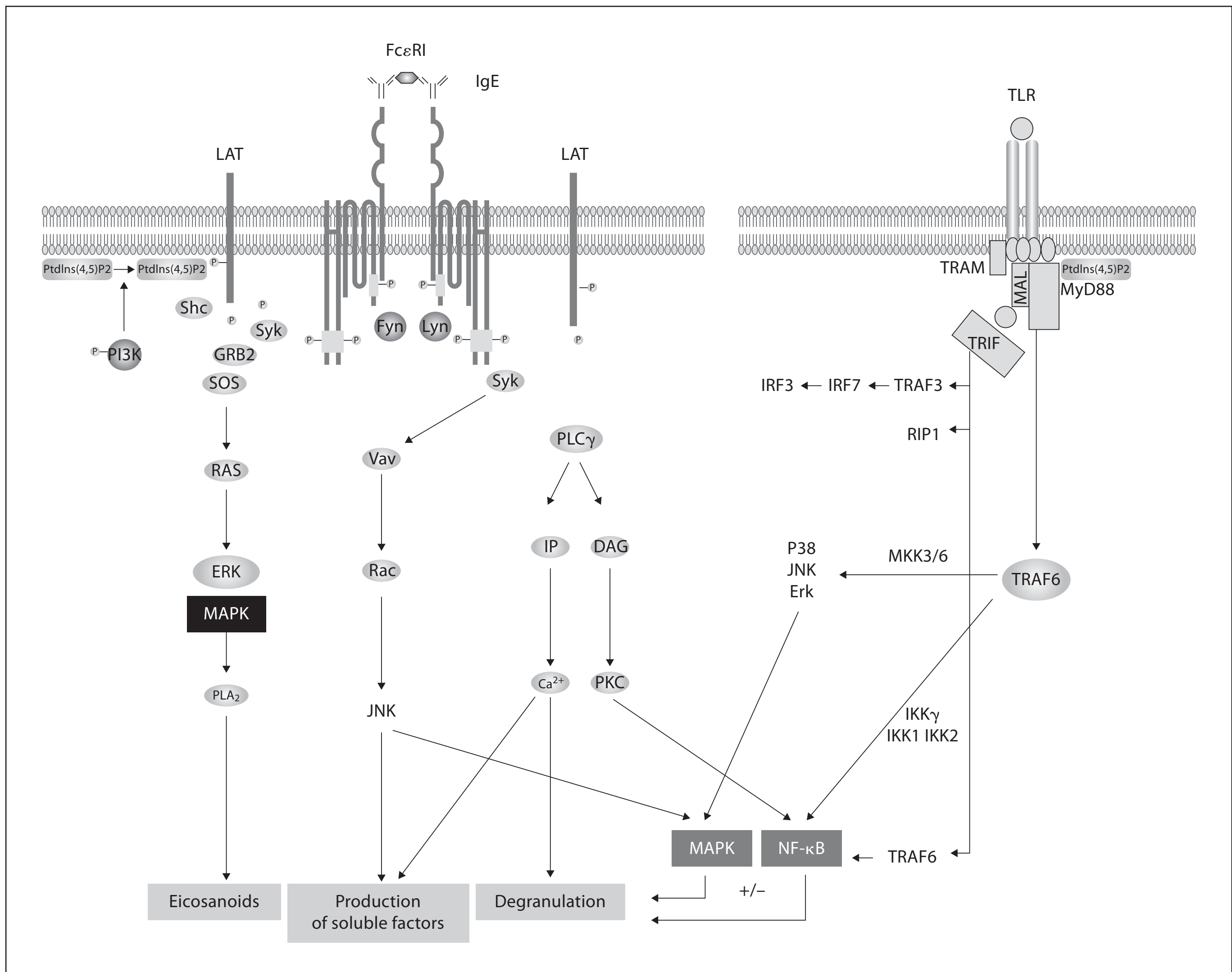

Fig. 1. Schematic diagram illustrating selected FcεRI and TLR signal transduction pathways.

identified in humans [5]. TLR1, TLR2, TLR4, TLR6 and TLR10 detect extracellular pathogen-associated molecular patterns, while TLR3, TLR7, TLR8 and TLR9 are expressed on endosomal membranes and recognize nucleosides, nucleotides and oligo- and polynucleotides derived from intracellular viral and bacterial pathogens [6]. TLR activation is comprised by ligand binding and several natural and synthetic TLR ligands have been identified so far [7]. TLR2 builds a complex with TLR1 or TLR6 and identifies bacterial lipopeptides, peptidoglycans and zymosan, TLR4 recognizes lipopolysaccharides and TLR5 bacterial flagellins. TLR3 detects double-stranded viral RNA, while single-stranded viral RNA is recognized by TLR7 and TLR8 and microbial DNA by TLR9 [7]. Intensive interaction and cross talk among TLRs and other surface receptors is a characteristic feature of TLRs [8]. In response to signaling via TLR2 and TLR4, the Toll/IL-1 receptor domain-containing adaptor protein (TIRAP), which is also called MyD88 adaptor-like, as well as MyD88 are required, while only MyD88 is required for other TLRs (fig. 1) [9, 10].

Both microbial antigens and allergens represent important trigger factors of allergic disorders and cells involved in allergic reactions are surrounded by a complex and heterogenous mixture of soluble and cell-bound ligands. Therefore, potential counterregulation and inter-

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Table 1. Summary of studies on TLR/IgE-R coactivation of mast cells

Species	Mast cell type	Receptor	Ligand	Effect	Ref. No.
Human	LAD2	TLR2	lipotechoic acid	suppressive on degranulation	18
Human	BMC	TLR4	ES-62	suppressive on degranulation	26
Murine	BMC	TLR2	Pam3CSK4[a]	suppressive on degranulation	19
Murine	BMC	TLR2/TLR4	LPS, P3C, MALP2, PGN	activating cytokine production	23, 24
Murine	BMC	TLR4	LPS	enhancing airway inflammation	25
Human	BMC	TLR4	*M. sympodialis*	enhancing IL-6 production	27

LAD2 = LAD2 human mast cell line; BMC = bone marrow-derived mast cells; TLR = Toll-like receptor; LPS = lipopolysaccharide; P3C = tripalmitoyl Cys-Ser-$(Lys)_4$; MALP2 = *Mycoplasma fermentas*; PGN = peptidoglycan.
[a] Optimal antigen dose.

action of TLRs with IgE synthesis and IgE receptor-mediated immune responses and the integration of the signal input from different receptors is essential to understand the mechanisms which either promote or prevent allergic immune responses.

Impact of TLR Activation on FcεRI-Mediated Signals of Mast Cells

FcεRI aggregation on mast cells induces a cascade of events including the synthesis and release of histamine and other mediators, which modulate cell adhesion, migration and signal transduction [1]. FcεRI cross-linking activates Lyn, which phosphorylates the ITAM of the FcεRIβ and FcεRIγ subunits (fig. 1). Further on, FcεRI aggregation induces the recruitment of the tyrosine kinase Syk, which phosphorylates the linker for the activation of T cells. This allows for recruitment of phospholipase C (PLC)γ via its Src-homology 2 domain [11]. PLCγ hydrolyzes membrane-bound phosphatidylinositol-4,5-bisphosphate to inositol triphosphate and diacylglycerol, which interfere with the mobilization of calcium ions, protein tyrosine phosphorylation and a cascade of additional events [11].

Additionally, activator protein 1 as mitogen-activated protein kinase pathways are involved [1, 12]. Together, these mechanisms induce the subsequent release and exocytosis of histamine and other preformed mediators of allergic inflammation by effector cells [13].

Mast cells have been known for a long time as key players of allergic reactions of immediate type and have in addition been identified to be important in the host defense against bacterial infections [14]. Their tissue distribution, expression pattern of surface receptors as well as capability to selectively produce a wide range of proinflammatory mediators predestine them to act as important networkers in these types of mechanisms. Different TLRs were demonstrated to be expressed by mast cells in relation to distinct mast cell types [15–17] (table 1). One of these TLRs expressed by human and murine mast cells is TLR2. The specificity of a number of ligands of TLR2 is connected with the heterodimerization of additional TLRs, namely TLR1 and TLR6. Depending on the type of ligand, TLR2 displays modulatory functions on FcεRI-mediated signaling of mast cells. Lipoteichoic acid downregulates the FcεRI expression of human mast cells of the human mast cell line (LAD2) in a dose-dependent manner and thereby attenuates FcεRI-mediated degranulation [18]. Suppression of mast cell degranulation, tyrosine phosphorylation and calcium mobilization was further shown to be promoted by the ligand Pam3CSK4, a synthetic tripalmitoyl lipopeptide binding to the TLR1/TLR2 heterodimer, while the ligand macrophage-activating lipopeptide-2, which binds to the TLR2/TLR6 complex did not exert such an inhibitory effect on the degranulation of murine bone marrow-derived mast cells [19]. However, both bacterial lipopeptides were able to synergize the production of the proinflammatory cytokine IL-6 by mast cells with suboptimal antigen doses [19]. These data imply a modulation of mast cell function after stimulation of mast cell TLR2 by respective ligands such as bacterial antigens and products. Moreover, protective effects exerted by TLR2 on FcεRI expression and degranulation of mast cells might be helpful in the context of therapeutic approaches, in which TLR2 ligands could be used to avoid unwanted mast cell activation and mediator release (table 1). Despite protective effects on mast cell degranu-

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lation, ligands to TLR2 and TLR4 were demonstrated to act synergistically on signals mediated by FcεRI resulting in reinforced cytokine production in bone marrow-derived mast cells from mice [20, 21]. Stimulation of TLR4 on bone marrow-derived mast cells also increased their capacity to produce Th2 cytokines, leading to enhancement of eosinophilic airway inflammation (table 1) [22]. Furthermore, products of parasitic filarial nematodes such as ES-62 have been shown to directly inhibit FcεRI-mediated mediator release of human mast cells. This effect is achieved by complexing of TLR4 and degradation of protein kinase C-α [23]. Moreover, a recent study demonstrated TLR2-related enhancement of IgE-mediated IL-6 release of mast cells stimulated with an extract of *Malassezia sympodialis (M. sympodialis*), [24]. Since the skin of patients with the chronic inflammatory skin disease atopic dermatitis is frequently colonized with this lipophilic yeast, and a subgroup of patients develops allergen-specific IgE against *M. sympodialis*, this interplay might be of relevance for the exacerbation of the inflammatory immune reaction in these patients. Thus, a synergistic amplification of proinflammatory mediators secreted by mast cells in response to coactivation of FcεRI with selected TLRs or specific TLR ligands might partially underlie the impairment of allergic inflammatory reactions. In this context, it is worth noting that several potential molecular intersection points between FcεRI and TLRs exist, such as the activation of the mitogen-activated protein kinase pathway or NF-κB signaling and others (fig. 1) [1, 12].

Counterregulation of FcεRI and TLR9 on PDC

PDC sense the environment for nucleic acids with the help of pattern-recognition receptors in the context of viral and microbial infections and thereby link innate and adaptive immune responses [25]. Human PDC are characterized by the expression of the IL-3 receptor α-chain (CD123) and the blood dendritic cell antigen (BDCA)-2 on their cell surface and are regarded as the only professional type 1 interferon-producing cells [26]. Upon stimulation with unmethylated CpG motifs or viral antigens, PDC release a large amount of IFN-α/β, which is of crucial importance for the defense against viral infections. Besides TLR7 and TLR9, human PDC bear a trimeric variant of the high-affinity receptor for IgE (FcεRI) on their cell surface [27, 28]. Similar to myeloid dendritic cells, the surface expression of FcεRI on PDC in the peripheral blood correlates directly with IgE serum levels and the atopic state of individuals [27]. Interestingly, the capacity to release IFN-α and IFN-β in response to TLR9 stimulation with CpG motifs is profoundly downregulated in PDC after FcεRI aggregation and allergen challenge in vitro, which implies a direct cross talk of FcεRI with TLR9 [27]. This cross talk might be of particular importance in atopic individuals, in which IgE-mediated allergen challenge might result in frequent FcεRI activation and subsequent downregulation of their capacity to release IFNα/β. Further evidence for a counterregulation of FcεRI and TLR9 derived from studies, which demonstrated a lower production of IFN-α by human blood dendritic cells from allergic individuals after TLR9 stimulation [29]. In addition, downregulation of FcεRI expression on PDC after TLR9 activation as well as reduced TLR9 expression after FcεRI cross-linking support the concept of a close cross talk of these structures on PDC [30]. On the molecular level, it was demonstrated that tumor necrosis factor-α released by PDC after FcεRI cross-linking downregulates TLR9 expression in an endogenous way [31]. Association of the FcεRIγ chain with BDCA-2 on PDC was identified as another possible molecular pathway underlying the reduced capacity of FcεRI-aggregated PDC to release IFN [32]. Based on this model, cross-linking of BDCA-2 resulted in the activation of the ITAM linked to the transmembrane adapter molecule FcεRIγ, leading to the induction of a B cell receptor (BCR)-like signaling pathway [32]. In this way, BDCA-2 cross-linking might suppress the capability of PDC to release IFN and other cytokines after TLR activation [32]. Another study revealed association of FcεRIγ with the immunoglobulin-like transcript 7 (ILT7) and suppression of the release of IFNs in response to TLR activation after ILT7 cross-linking as yet another mechanism connecting FcεRI with TLRs [33].

This implies that TLR-mediated mechanisms of the innate immune system directly interact on different levels with IgE-dependent immune mechanisms and that PDC represent an important link between innate and adaptive immunity in this context. Besides a direct counterregulation of FcεRI and TLR9 on PDC, other studies provide evidence for a modulation of immune responses of FcεRI-bearing human blood monocytoid DC (BMDC) and TLR-bearing PDC [34]. Coculture experiments of BMDC and PDC demonstrated that IL-10 secretion induced by FcεRI cross-linking of BMDC was further enhanced by IFN-α, released by TLR9-activated, cocultured PDC [34]. These data illustrate that TLR and FcεRI do not interact on the single cell level only. Moreover, the data imply that close interactions of different TLR- and

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FcεRI-bearing cells exist in vivo, which might be regulated by the availability of receptor ligands and the proportion of the respective FcεRI and/or TLR9-bearing cell subtypes in the microenvironment. Taken together, the reduced capability of PDC to release IFN in response to TLR stimulation by viral antigens after FcεRI activation/allergen challenge might explain in part the increased susceptibility of allergic patients to viral infections observable in vivo [35, 36]. Detailed knowledge of the different components of this complex counterregulation would be indispensable to understand in which way allergic immune responses act on the defense of viral infections, and whether viral infections rather reduce or increase the risk for the manifestation and impairment of allergic diseases.

Impact of TLR Ligation on the IgG/IgE Class Switch and Antibody Production of B Cells

Stimulation of B cells by antigens through the BCR combined with T cell help results in the proliferation and differentiation of antigen-specific naïve B cells into memory B cells and plasma cells [37]. The nature of the B cell response is regulated by activation of BCR combined with signals of other receptors, which enables B cells to specifically react to environmental stimuli [37]. Recently, it was demonstrated that human naïve B cells upregulate TLRs upon BCR activation [38]. TLRs are differentially expressed on human and mouse B cells. Human memory B cells express for instance TLR1, TLR2, TLR6, TLR7, TLR9 and TLR10 [38, 39]. Intriguingly, stimulation of TLR9 with unmethylated CpG motifs activated human naïve B cells and enhanced the B cell response [40]. Further on, stimulation of B cells with TLR9 ligands induced expression of the transcription factor T-bet [41] and initiated germline Cγ1, Cγ2 and Cγ3 gene transcription [42]. As a result, CpG stimulation of B cells inhibited the IL-4-and CD40-dependent IgG1/IgE class switch [43]. In addition, stimulation of B cells with TLR7 or TLR9 ligands profoundly increased IgA production in vitro, while TLR7 or TLR9 induced IgA production was suppressed in the presence of IL-4 or sCD40 in favor of an increased IgE and IgG4 production [44]. Together, these data suggest that TLR stimulation of B cells might lead to the inhibition of the IgG/IgE class switch and suppress the IgE production. Possibly, this TLR-mediated coregulation of the antibody production of B cells contributes to some degree to the prevention of allergic immune responses in vivo.

FcεRI-TLR Cross Talk Is of Relevance in Allergen-Specific Immunotherapy

The immunostimulatory properties of TLR ligands and their capability to attenuate Th2 immune responses, while enforcing Th1 immune responses were demonstrated in studies using different murine and human model systems [45]. Together with the multifaceted interaction of TLRs with FcεRI and mechanisms involved in the regulation of mast cell and PDC functions as well as IgE synthesis mentioned above, TLR ligands represent interesting tools for allergic vaccines. As an example, targeting TLR9, immunostimulatory sequence DNA linked to the allergenic component of ragweed pollen allergen promoted Th1 cytokine expression of PBMC in vitro [46]. Further on, the efficacy of TLR9 ligands as monotherapy or combined with vaccines is currently under investigation in murine asthma models [8]. In addition, a first placebo-controlled pilot study of 25 adult patients with allergic rhinitis revealed significant clinical improvement in the subgroup of patients treated with a ragweed pollen antigen conjugated to a phosphorothioate oligodeoxyribonucleotide-immunostimulatory DNA sequence as a ligand to TLR9 [47]. These in vivo and in vitro findings strongly support the hypothesis of CpGs as putatively helpful adjuvants in allergen immunotherapy.

As another example, the TLR4 ligand monophosphoryl lipid A (MPL) was shown to enhance IgG2 antibody responses and to reduce IgE antibody production when combined with glutaraldehyde-modified ragweed pollen allergen in animal models [48]. In line with these findings, MPL applied together with an allergen to PBMC of grass pollen-allergic individuals profoundly increased the IFN-γ production of the cells, while the IL-5 production decreased [49]. Further on, $Fc\varepsilon RI^{pos}$ human dendritic cells isolated ex vivo and stimulated with MPL displayed enhanced protolerogenic properties in terms of the induction of suppressive cytokines such as IL-10 and TGF-β in cocultured T cells as well as Foxp3-expressing regulatory T cells [50]. Together, these in vitro data strongly argue for a positive effect of MPL on the intended immune deviation and induction of tolerogenic mechanisms during allergen-specific immunotherapy in vivo. Moreover, the combinatory effect of allergens and the TLR4 ligand MPL might form the basis for the positive results observable after the treatment of patients with allergic rhinitis with commercially available allergen vaccines, which contain MPL as adjuvant [51].

Beside TLR4 and TLR9 ligands, several other TLR ligands are currently under intensive investigation in ex-

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perimental and clinical studies to rule out their value as putative adjuvants in allergen-specific immunotherapy [45].

Concluding Remarks

Insights into the network of FcεRI/IgE-mediated mechanisms with signals routed via TLRs are of substantial interest for the understanding of the prevention, manifestation and treatment of allergic diseases. Although immune cells are under the influence of an abundance of different ligands in vivo, most of the in vitro studies focus on the nature of immune responses evolving from the stimulation of a single receptor. However, the coordination and processing of combinatory or sequential stimulations of different receptors on the same cell is decisive for the outcoming immune response. The data available so far about FcεRI/TLR coregulation on mast cells, PDC and B cells provide first exciting insights into the versatile character of the IgE-TLR network. However, these data represent only the tip of an iceberg, since detailed information about comparable mechanisms on monocytes, myeloid dendritic cell subtypes or other FcεRI-bearing cells or the impact of further TLRs and TLR ligands on FcεRI signaling and IgE synthesis is still missing.

Taken together, costimulation of TLRs on FcεRI-bearing cells as summarized here might contribute to the protective effect of antimicrobial antigens on the maturation of the immune system and prevent the organisms to some degree from the manifestation of allergic immune responses. However, under certain circumstances, concomitant stimulation of FcεRI and TLR might amplify the proinflammatory immune reaction due to a synergistic effect on the release of proinflammatory mediators or increase the susceptibility toward bacterial or viral infections by the active downregulation of immune responses involved in host defense.

Finally, the positive effects evolving from TLR ligands on immune responses of the immediate type driven by effector cells, their properties to enforce the protolerogenic features of antigen-presenting cells, their positive influence on Th1-dominated immune deviation as well as their impact on antibody production of B cells hold promise that TLR ligands might be valuable tools to develop protective vaccines for early prevention of allergic diseases and substantially contribute to the improvement and optimization of allergen-specific immunotherapy strategies in the near future.

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